REMARKS

Applicant respectfully requests reconsideration. Claims 42-53, 59-69, 71-73 and 75-80 were previously pending in this application. No claims have been amended, canceled or added. As a result, claims 42-53, 59-69, 71-73 and 75-80 are still pending for examination with claims 42 and 71 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 42-53, 59-69, 71-73, 75-80 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has dismissed the arguments presented by Applicant because it is asserted that practice of the invention would require undue experimentation. It is concluded that "taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation." Applicant's disagree.

The standard for enablement is assessed at the effective filing date of the patent application. The sufficiency of a disclosure "must be judged as of the filing date."[1] Documents pertaining to later filed art are not permitted to be used for the purposes of either establishing or disproving enablement. The court in *In re Hogan* rejected the use of post-filing documents to reject a claim under §112, ¶1.[2] The court noted that the law approves "use of later publications as evidence of the state of art existing on the filing date of an application," but that the approval "does not extend, however, to the use of a later . . . publication disclosing a later . . . existing state of the art in testing an earlier . . . application for compliance with s 112, first paragraph."[3] The court went on to add that "the difference may be described as that between the permissible application of later knowledge about art-related facts existing on the filing date and the impermissible application of later knowledge about later art-related facts . . . which did not exist on the filing date."[4]

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[1] *In re Glass*, 492 F.2d 1228 at 1232 (CCPA 1974).
[2] 559 F.2d 595 at 605 (CCPA 1977).
[3] *Id.*
[4] *Id.*

The majority of references discussed with respect to enablement by both Applicant and Examiner in the prosecution history are post-filing references. While the use of such references is permissible, the purpose of such references is to provide evidence with respect to the predictability in the art at the time of the invention. In order to clarify the distinction, Applicant's address separately the post-filing and pre-filing references.

State of the Art at the time the patent Application was Filed.

In response to the prior office action Applicant presented some evidence of the state of the art at the time the application was filed and also provided a discussion of how such art related to the data that was provided in the specification. Applicant asserts that in view of what was known in the art at the time of the invention and the data and teachings provided in the specification, one of ordinary skill in the art would have had a reasonable expectation that CpG oligonucleotides were useful for treating cancer. These arguments are summarized below. It is requested that the examiner specifically consider and address these arguments.

At the time the patent application was filed it was known in the art that induction of interferon-γ (IFN-γ), IL-12, and IL-6 as well as NK cell activation was useful in the treatment of cancer. The following summaries of references published prior to or around the priority date of the instant application describe the state of the art with respect to immune system activation and the treatment of cancer. Each reference has previously been made of record.

Trinchieri et al., Blood, V.84, December 15, 1994, p. 4008 is a review article describing IL-12 in the production of cytotoxic lymphocytes. Page 4021 describes the role of IL-12 in anti-tumor immunity. Specifically, it is taught that "studies using transplantable tumors in experimental animals have shown a dramatic affect of IL-12 in decreasing tumor growth and metastasis formation and in significantly delaying death.[134] Systemic Daily Treatment (5 days per week) had a significant inhibitory affect on the growth of metastasis induced by intravenous injection of B16 melanoma cells and efficiently inhibited the growth of subcutaneously injected tumors, even when treatment was initiated two weeks after tumor inoculation.[123] An inhibitory affect of IL-12 on tumor growth, with a greater than two-fold increase in survival of inoculated animals, was also observed with the reticulum cell sarcoma M5076 and with the renal cell adenocarcinoma renca.[134]

In this latter tumor, complete remission, especially with peritumoral injection of IL-12, was observed in some animals; reinjection of the renca cells in the "cured" animals resulted in delayed growth of the tumor, suggesting that IL-12 may induce a memory immune response against the tumor.[134]" (Paragraph spanning 4021-4022).

Brunda et al. Journal Leukocyte Biology, V.55, February 1994 is a review article describing IL-12. Pages 285-286 of Brunda et al. describe the use of IL-12 in vivo in numerous murine tumor models. It is taught that "a large body of experimental evidence has now been accumulated demonstrating that IL-12 has potent antimetastatic and antitumor activity in a number of murine tumor models. The therapeutic activity of IL-12 has been observed in four of four murine metastasis models, including both pulmonary and hepatic metastases." (P. 285, first column, last paragraph).

U.S. Patent No. 4,883,662 issued on November 28, 1989, describes an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells. (Abstract). In the summary of the invention it is taught that "it has been established that increasing such natural killer cells is an important component of the immune system, and that accordingly the present method should be a decided advantage in cancer treatment. ...furthermore, it is believed at least two-fold increase in natural killer cells should be affected in order to obtain meaningful treatment results."

Hayashi et al., Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205, describes immunotherapy for the treatment of cancer. The abstract teaches that immunotherapy with BCG-CWS results in IFN-γ induction. It is further taught that cancer patients experiencing IFN-γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN-γ induction, who died after a short period.

The above described papers were published prior to or around the priority date of the instant application. The papers establish that one of skill in the art would have recognized the utility of a drug which is effective in inducing IL-12, IFN-γ and NK cell activation as a compound which would be useful in the treatment of cancer. Thus, at the time of the invention the data presented in the specification would have been sufficient to demonstrate to one of skill in the art that unmethylated CpG oligonucleotides are useful in the treatment of cancer. Applicant has presented

sufficient evidence to establish the correlation between the induction of the disclosed cytokines as well as NK cell activation and the treatment of cancer.

Post-Filing Art

Although some of the post-filing art suggests unpredictability, the post-filing art as a whole supports the effectiveness of CpG oligonucleotides in the treatment of cancer. An important factor to consider is that currently at least 4 different CpG oligonucleotides are being tested in clinical trials in the therapy of cancer. If the treatment of cancer using CpG oligonucleotides were so unpredictable, in the years following the invention, that the claims were not enabled, it seems highly unlikely that the FDA and regulatory agencies in other countries would allow testing of these compounds in humans for cancer therapy. When the issue of predictability is viewed, considering the post-filing art as a whole, one of skill in the art would conclude that the practice of the invention would not have required undue experimentation at the time the application was filed.

The examiner has concluded that subsequent publications clearly recognize the obstacles in treating cancers comprising oligonucleotides containing CpG motifs. (Office Action page 6). The Examiner's points with respect to several post-filing references are each addressed below. The teachings of these post-fling references must be considered in their entirety. To the extent that the references include inconsistent statements, the teachings contained therein must be balanced carefully to reach a conclusion on the predictability or unpredictability of a claimed invention at the time the application was filed. When each of the references is considered in their entirety it is clear that the references support feasibility of the claimed invention, particularly when the references are specifically addressing the use of CpG oligonucleotides in therapy. Balancing the teachings of this group of references as a whole, one of skill in the art would be led to the conclusion that at the time of the invention, the use of the claimed invention could be achieved without undue experimentation particularly when considered in the context of the specification and the knowledge of the skilled artisan at the time of the invention.

The Examiner has asserted that Krieg (Nat. Revs. 2006 v. 5 p. 471) teaches it is necessary to use combinations in cancer therapy and thus the treatment of cancer is not completely resolved. Initially, Applicant notes that a therapeutic treatment need not be "completely resolved" for an

invention to be enabled. A significant amount of experimentation to perfect an invention is acceptable as long as such experimentation is not undue and is routine. Further, the Examiner has not indicated where such a statement is found in Krieg (2006). Table 2 of Krieg (2006) provides a list of monotherapy, vaccine and combination therapies using CpG oligonucleotides. On page 477 column 2 last paragraph it is stated "In relatively small tumours CpG monotherapy can be sufficient to induce a T-cell mediated rejection of established tumours; however, to induce rejection of larger tumours the CpG ODN often needs to be combined with other effective antitumour strategies." To conclude based on this sentence that a reference teaches combinations are necessary is inaccurate. This statement actually teaches that immunotherapy appears to be sufficient for treating smaller tumours. The claims are not limited to the treatment of large tumours. Further, the claims are not limited to monotherapy. The addition of other therapeutic agents is encompassed by the broadest claims. Further claims 43, 44, 68, 71, and 79-80 all specifically recite the combination of a CpG ODN with a second therapeutic agent.

Further, the overall teachings of Krieg (2006) support the therapeutic value of CpG oligonucleotides in the treatment of diseases such as cancer. Krieg (2006) describes "encouraging evidence for the capacity of TLR9 activation to induce a TH1-like cytokine response in human cancer patients has been reported recently in studies in dendritic cells isolated from primary human tumours[100] and in lymphoma patients treated with a CpG ODN alone or together with an antitumour antibody." (Page 477, second column, last paragraph). In Table 2 on page 478 of Krieg, the human clinical trials being conducted or completed as of 2006 are listed. The clinical trials for cancer include a phase I monotherapy, a phase II vaccine therapy, and a phase I, II and III combination therapy.

The Examiner has also dismissed as not being persuasive Applicant's discussion of the clinical trials described in Krieg 2006 and other references because "the references are directed towards viral studies, and further the art demonstrates T cell responses and immunogenicity of only one CpG dinucleotide." This is not accurate. As stated in Applicant's last response to Office Action, a 2007 review article, Krieg, J. Clin Invest. 117, p. 1184, 2007, describes a summary of TLR9 agonists in cancer therapy. Table 2 lists published *oncology clinical trials* with TLR9 agonists and Table 3 lists ongoing *oncology clinical trials* with TLR9 agonists. Applicant presented

a significant amount of evidence related to cancer clinical trials. The fact that only a few specific CpG oligonucleotides are being used in clinical trials is not evidence that other CpG oligonucleotides don't work. The studies are being conducted in humans It is not feasible to study numerous oligonucleotides in humans. However, a significant amount of data has been generated in animal models using numerous CpG oligonucleotides over the years. When read in its entirety Krieg 2006 is supportive of the claimed invention.

Weiner (Leukocyte Biology, 2000, 68: 455-465) was cited as indicating "there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy." It is further stated that despite this promise, Weiner teaches that we don't understand the molecular mechanisms responsible for the effects of CpG ODN. (Office Action Page 6). Knowledge of the mechanism of action isn't necessary, particularly in view of the detailed knowledge at the time the patent application was filed of the cellular effects of CpG oligonucleotides. The patent application identifies consistent changes in the immune system at the cellular level that occur in response to CpG administration and which are therapeutically relevant. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner, such as that noted by the Examiner, are consistent with enablement of the claimed invention.

Krieg (Nature, 1995, 374: 546-549) was also cited for teaching that CpG oligonucleotides can be used in immunotherapy of tumors, though many or most may be NK resistant. Applicant cannot identify such a teaching in Krieg et al. Page 117, column 2 is cited in support of this teaching. However the reference is found on pages 546-549. Clarification of the support for this assertion is requested.

On pages 7-8 of the Office Action the Examiner maintains that Agrawal et al (Trends in Mol Med. 2002, 8: 114-121) teaches that different effects are observed with different CpG ODN and that Ballas et al (J. of Immunology, 2001, 167:4878-4886) teaches a single ODN can't be used for all cancers. CpG ODN may produce variant results, with some ODN producing more potent immune stimulation and others preferentially activating certain subsets of immune cells. However, as described in the specification, Applicant established that CpG oligonucleotides as a class of

molecules produce an immune response that collectively is useful in the treatment of disease. The fact that specific CpG ODN may involve further fine-tuning, does not negate enablement. The fact that an invention may involve fine-tuning or optimization following the invention does not "clearly indicate" that the invention was not enabled. "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re: Angstadt 537 F.2D 498, 504, 190 USPQ 124, 129, (CCPA 1976)" "The fact the experimentation may be complex does not necessarily make it undue. If the art typically engages in such experimentation. In re: Certain limited-charge cell culture microcarriers, 221 USPQ 1165, 1174) Int'l Trade Comm'n 1983)." (MPEP Section 2164.01). The use of any drug in human patients requires further fine-tuning. Even commercially available FDA approved drugs are subject to further research and development. Experiments involving fine-tuning to understand the medicinal chemistry potential are not undue experimentation.

On balance the teachings of the prior art as well as the post-filing art overall are consistent with and support the use of CpG oligonucleotides in the treatment of cancer based on the data and descriptions in the patent application as filed. Miscellaneous statements in references referring to future work, fine-tuning, optimization or additional experimentation to prove clinical efficacy do not support a finding of unpredictability of the claimed invention. As shown in the specification, Applicant generated pre-clinical data on CpG oligonucleotides that demonstrated activity consistent with the treatment of cancer. Currently there are a number of clinical trials being conducted with CpG oligonucleotides, including trials for the treatment of cancer with CpG oligonucleotides.

At the time of the filing of the patent application, Applicant described a class of molecules useful for the treatment of cancer. Applicant's fundamental invention is based at least in part on the discovery that the immune system detects bacterial DNA by the presence of unmethylated nucleotides, which can be present in a wide variety of base contexts. The applicant was the first to recognize that these immune activating effects of bacterial DNA could be reproduced using synthetic oligonucleotides containing unmethylated CpG. The fact that an author suggests that the medicinal chemistry of this class of molecules needs further fine-tuning at a later date does not indicate that the claimed invention lacks enablement. Even after drugs are used successfully in humans, researchers continue to do research and fine-tune various aspects of the drug. Optimization

or preferential selection of species at a later point in time does not render the use of a genus of compounds unpredictable at an earlier time point.

Accordingly, withdrawal of the rejection of claims 42-53, 59-69, 71-73, and 75-78 under 35 U.S.C. §112 is respectfully requested.

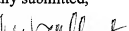
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70021US01.

Dated: August 4, 2008

Respectfully submitted,

By 

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000